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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,173	06/24/2004	Katsuhito Takahashi	4439-4022	3299

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EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
06/03/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/500,173	TAKAHASHI ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,7,20,21,23-26,35 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,7,20,21,23-26,35 and 36* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/28/2008 has been entered.

Claims 2-5, 8-19, 22, and 27-34 have been cancelled. Claims 1, 20, and 35 have been amended.

Claims 1, 6, 7, 20, 21, 23-26, 35, and 36 are pending and under examination.

2. All rejections pertaining to claims 9-13 and 18 are moot because Applicant cancelled the claims in the response filed on 04/28/2008.

The rejection of claims 1, 6, 7, 20, 21, 23-26, 35, and 36 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is withdrawn in response to Applicant's amendments to the claims filed on 04/28/2008.

The rejection of claims 1, 6, 7, and 20-34 under 35 U.S.C. 112, first paragraph, as introducing new matter, is withdrawn in response to Applicant's amendments to the claims filed on 04/28/2008.

The rejection of claims 1, 6, 7, 9-13, 18, 20, 21, 25, 35, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al. taken with both Chung et

al., Yamamura et al., in further view of Van Meir et al. (PGPUB 2005/0074430, of record) is moot because Applicant cancelled claims 9-13 in the response filed on 04/28/2008.

Specification

3. The disclosure is objected to because of the following informalities: improper English translation and arrangement (see the non-final Office action of 04/21/2006). However, upon Applicants request filed on 07/21/2006, the submission of a re-translated version of the specification is deferred.

Claim Objections

4. Claim 1 is objected to because the recitation of "using the expression of the LacZ gene and the EGFP gene integrated in the vector as an index" does not make sense in the context of the claim. Correction to " using the expression of the LacZ gene and the EGFP gene integrated in the vector as an index to identify the recombinant HSV vector" is suggested.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been

obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1, 6, and 7 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 7 of copending Application No. 10/477,797 in view of both Martuza (U.S. Patent No. 5,728,379, of record) and Wagstaff et al. (Gene Therapy, 1998, 5: 1566-1570). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are drawn a herpex simplex virus (HSV) vector comprising the thymidine kinase gene (*tk*) and a DNA fragment comprising the calponin promoter, the ICP4 gene downstream to the calponin promoter, the EGFP gene linked downstream to the ICP4 gene via an IRES, and *lacZ* integrated upstream to the calponin promoter; the vector is obtained by inserting the DNA fragment into the ribonucleotide reductase gene

locus (claim 1). The vector further comprises the 4F2 enhancer integrated upstream to the calponin promoter (claims 6 and 7).

The application claims 1 and 7 recite an HSV vector having a cDNA fragment comprising the calponin promoter, the ICP4 gene downstream to the calponin promoter, and the 4F2 enhancer integrated upstream to the calponin promoter. The specification defines that the vector contains *lacZ* upstream to the calponin promoter and that the DNA construct is inserted into the *tk* locus (see Fig. 3). Therefore, the application claims are drawn to a vector comprising the construct inserted into the *tk* locus and not into the ribonucleotide reductase gene locus, as recited by the instant claims. However, obtaining HSV vectors by inserting constructs into the ribonucleotide reductase gene locus is taught by the prior art. For example, Martuza discloses HSV vectors for use in the specific killing of tumor cells through the use of tissue specific promoters., wherein the vectors have an intact *tk*, wherein the ribonucleotide reductase gene is disrupted by insertion of constructs, and wherein vector replication can be suppressed by using ganciclovir (Fig. 4 and 5, column 5, lines 1-9 and 39-45, column 7, lines 20-35, column 21, lines 40-60, column 25, lines 51-55, column 33, lines 48-6, Example 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the application claims by inserting the DNA fragment into the ribonucleotide reductase gene locus to obtain a vector with an intact *tk*, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to suppress vector replication when needed. One of skill in the art would have been motivated to insert the construct into the ribonucleotide reductase gene locus because

Martuza teaches that ribonucleotide reductase gene locus disruption is essential for therapeutic vectors because it results in vectors less likely to replicate in normal cells and in vectors with increased sensitivity to acyclovir (column 22, lines 1-3 and 24-40, column 25, lines 57-62). One of skill in the art would have been expected to have a reasonable expectation of success in doing so because the art teaches that therapeutic HSV vectors can be successfully obtained by inserting desired constructs into the ribonucleotide reductase gene locus. The patent claims do not recite inserting EGFP downstream to ICP4 via IRES. However, at the time the invention was made, the use of IRES to obtain bicistronic HSV vectors expressing GFP as a reporter to identify the transduced cells was taught by the prior art (see Wagstaff et al., Abstract, p. 1567, Fig. 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the application claims by inserting GFP downstream to ICP4 via IRES to achieve the predictable result of identifying the transduced cells.

Since the application claims embrace all limitations of the instant claims, the application claims and the instant claims are obvious variants of each other.

Applicant has requested that the obvious-type double patenting rejection set forth by the Examiner be held in abeyance. The Applicants' comments are acknowledged, however the rejection is maintained until a Terminal Disclaimer is filed or the claims are amended to obviate the rejection.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1, 6, 7, 20, 21, 25, 35, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al. (U.S. Patent No. 5,728,379, of record), in view of each Chung et al. (J Virol, 1999, 73: 7556-7564, of record), Yamamura et al. (Cancer Res 5/2001, 61: 3969-3977, of record), Wagstaff et al., and Foster et al. (J Virol Methods, 1998, 75: 151-160).

Martuza et al. teach an HSV vector comprising a DNA fragment comprising tissue-specific promoters, the ICP4 gene downstream to the tissue-specific promoter, *lacZ* upstream to the tissue-specific promoters derived from genes highly expressed in tumor cells, and tissue-specific enhancers upstream to the tissue-specific promoters, wherein the vector is obtained by inserting the DNA fragment into the HSV genome and wherein the vector expresses therapeutic factors in a tissue-specific manner; the DNA fragment could be inserted into the *tk* locus or into a locus other than the *tk* locus, wherein the vector with intact *tk* is sensitive to ganciclovir (claims 1 and 6) (column 4, lines 40-59, Figure 1 and its Brief description at column 6, lines 42-45, column 4, lines 30-67, column 11, lines 4-16, column 25, lines 39-56, claims 1-3, 12, and 13). Therefore, Martuza et al. also teach a method for expression of a therapeutic factor in tumor cells by using an HSV vector, wherein the HSV vector does not replicate in normal cells (claims 20 and 25). In addition to the above, Martuza et al. teach the use

of ganciclovir to suppress the replication of their HSV vector, i.e., they teach a method for suppressing the expression of the gene encoding the therapeutic factor (claim 21) (column 7, lines 20-35, column 25, lines 51-55, column 33, lines 48-64). Martuza et al. teach their HSV vector as comprising a disrupted ribonucleotide reductase gene, wherein disruption takes place via *lacZ* insertion into the ribonucleotide reductase gene locus by homologous recombination, i.e., co-transfecting the *lacZ*-containing fragment with a viral DNA into Vero cells (i.e., cells which do not express ICP4 and which contain transcription factors that activate the calponin promoter, see Example A of the instant specification), and purifying clones by limiting dilution (claims 1, 35, and 36) (Fig. 4 and 5, column 5, lines 1-9 and 39-45, column 21, lines 40-60, Example 1). Martuza et al. teach that ribonucleotide reductase gene disruption is essential for therapeutic vectors, wherein disruption results in increased sensitivity to acyclovir and ganciclovir and wherein the ribonucleotide reductase-disrupted vectors are less likely to replicate in normal cells (column 22, lines 1-3 and 24-40, column 25, lines 57-62).

Although Martuza et al. teach that the DNA fragment comprising ICP4 operably linked the tissue specific promoter can be inserted by homologous recombination in any location of the HSV genome, they do not specifically teach inserting into the ribonucleotide reductase locus (claims 1 and 35). However, inserting DNA constructs into the ribonucleotide reductase locus to obtain therapeutic HSV vectors is taught by the prior art. For instance, Chung et al. teach insertion of a DNA comprising a tissue specific promoter operably linked to a gene essential for HSV virulence into the ribonucleotide reductase locus (p. 7558, Fig. 1, p. 7557, column 1, second paragraph

and column 2, *Results*). Based on these teachings and on the teachings of Martuza et al. that the DNA fragment can be inserted at any locus in the HSV genome, it would have been obvious to one of skill in the art, at the time the invention was made, to insert the DNA fragment comprising ICP4 gene operably linked the tissue specific promoter into the ribonucleotide reductase locus, to achieve the predictable result of obtaining a vector suitable for gene therapy, which vector does not replicate in the normal cells and which vector exhibits increased sensitivity to acyclovir and ganciclovir. With respect to the limitation of cloning without agarose overlay (claim 35) it is noted that the patentability of the composition does not depend on the method of obtaining it (see MPEP 2113 [R-1]). The instant end product (i.e., the HSV vector) is identical to the end product taught by the combined teachings above, regardless of whether cloning takes place with or without agarose overlay. Applicant did not provide any evidence that cloning in the absence of agarose overlay results in an HSV vector which is structurally different from the HSV vector taught by the cited prior art.

Although Martuza et al. and Chung et al. teach a cell-specific promoter and an enhancer, they do not specifically teach the full length calponin promoter or the 4F2 enhancer (claims 1 and 7). Yamamura et al. teach the calponin promoter driving the expression of the ICP4 gene and the 4F2 enhancer, wherein the 4F2 enhancer is integrated upstream to the calponin promoter and wherein the 4F2 enhancer further upregulates ICP4 expression (p. 3970, column 1, fourth full paragraph and Figure 1A and 1B, p. 3972, column 1, first paragraph). Yamamura et al. also teach that calponin is highly expressed in a variety of human soft tissue and bone tumors (Abstract, p. 3969,

column 2, p. 3976, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the HSV vector of Martuza et al. by using the calponin promoter together with the 4F2 enhancer, with a reasonable expectation of success. One of skill in the art would have been motivated to use the calponin promoter in order to target therapeutics to the human soft and bone tumor cells. One of skill in the art would have been motivated to use the 4F2 enhancer because Yamamura et al. teach that insertion of the 4F2 enhancer upstream of the calponin promoter increases the transcriptional activity of the calponin promoter (p. 3972, column 1). One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a vector because the art teaches that such vectors can be successfully made and because Martuza et al. teach that promoters derived from genes highly expressed in tumor cells can be successfully used to specifically drive vector replication in tumor cells.

Martuza et al., Chung et al., and Yamamura et al. do not teach inserting the EGFP gene downstream to the ICP4 gene via IRES (claims 1 and 35). However, at the time the invention was made, the use of IRES to obtain bicistronic HSV vectors expressing GFP as a reporter to identify the transduced cells was taught by the prior art (see Wagstaff et al., Abstract, p. 1567, Fig. 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the application claims by inserting GFP downstream to ICP4 via IRES to achieve the predictable result of identifying the transduced cells. While Wagstaff et al. teach GFP and not EGFP, it is noted that EGFP was known and used in the prior art (see Foster et al., Abstract).

Therefore, one of skill in the art would have known to substitute GFP with EGFP to achieve the predictable result of identifying transduced cells.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant asserts that the claimed invention is not made obvious by the combination of Martuza, Yamamura and Chung. Martuza teaches an HSV vector with DNA construct that has a tissue specific promoter and ICP4 gene inserted in a thymidine kinase locus, which results in an inactive TK gene. However, because the vector does not have the TK gene, the vector would not be applied in a clinical environment due to safety issues, whereas, if the vector contains the TK gene, it is sensitive to ganciclovir and acyclovir (see paragraphs 76 and 77 of the published specification). Therefore, TK-deleted recombinants can easily be identified and selected by culturing the HSV vectors on a medium that contains ganciclovir and acyclovir. To arrive at the claimed invention, the Examiner looks to Yamamura for support of a construct of a calponin promoter and ICP4 gene, which also inserted in the TK locus and Chung for support of inserting a tissue-specific promoter and ICP4 gene construct within the ribonucleotide reductase gene locus. Assuming arguendo that the teachings of Martuza, Yamamura and Chung could be combined as suggested by the Examiner, one of skill in the art would still not arrive at the claimed invention. The claimed HSV vector is obtained by inserting a DNA fragment comprising the region containing a full length promoter of the human calponin gene, the ICP4 gene, and two

marker genes (*lacZ* and EGFP) into the ribonucleotide reductase (RR) gene locus. Applicant points out that by using the claimed DNA fragment, the altered HSV vector can be identified because this cDNA expresses a green fluorescent protein (EGFP) that shows fluorescence. Whereas, Martuza, Chung and Yamamura alone or in combination do not teach each and every element of the claimed invention, i.e., a DNA fragment comprising two specific reporter genes inserted within the RR locus. In fact, Martuza and Yamamura utilize the inactivation of TK gene as a marker or index, whereas Chung utilizes the removal of the LacZ gene from RR locus as a marker or index. Thus, even in combination, the cited art would not produce the claimed HSV vector that has a full length promoter of the human calponin gene, the ICP4 gene, and two reporter genes inserted in the ribonucleotide reductase (RR) gene locus. Furthermore, applicants assert that one skilled in the art could not combine the teachings of Martuza and Yamamura with Chung without a great deal of undue experimentation. Martuza produced a cell-specific expression replication vector ptkAL-ALI4 where a DNA fragment coupling ICP4, albumin promoter and lacZ is inserted into the thymidine kinase (TK) gene locus by homologous recombination (i. e., tumor cell-specific proliferation due to TK ablation; liver tumor cell-specific proliferation due to ICP4 expression by albumin promoter). Martuza, however, did not succeed in producing a cell-specific expression replication vector where a DNA fragment coupling ICP4, albumin promoter and lacZ is inserted into the ribonucleotide reductase (ICP6) gene locus by homologous recombination. Martuza produced only the replicable HSV-1 vector G207 which lacks copies of the γ34.5 gene involved in replication in neural cells

and in which only LacZ gene is inserted in the ribonucleotide reductase (ICP6) gene locus (tumor cell-specific proliferation due to TK ablation; non cell-specific due to lack of ICP4 gene coupling to a cell-specific promoter). Chung, on the other hand, describes a predetermined viral gene γ34.5 that can be combined with the B-myb promoter and inserted within the RR gene locus. Chung does not teach how to insert other tissue-specific promoters, e.g., albumin promoter of Martuza, in conjunction with the ICP4 gene and LacZ. Applicant asserts that the construct of Martuza, i.e., ICP4, albumin promoter and lacZ, is not the same as the construct of Chung, i.e., viral gene γ34.5 and B-myb promoter, and are not interchangeable as suggested by the Examiner. Applicant asserts that one skilled in the art could not make a construct of Martuza within the RR locus as taught by Chung without significant attempts because any one of the lacZ gene, a cell-specific promoter, and an ICP4 gene may undergo ablation when attempting to construct a herpes viral vector as claimed, or because of the difficulty in cloning the vector even when such a vector with appropriate recombination of the above three elements has been produced. Therefore, none of the references, either alone or in combination, discloses all the elements to produce the claimed HSV vector and one of skill in the art would not look to Chung to overcome the deficiencies of Martuza and Yamamura.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

Applicant's argument that Martuza et al. only teach insertion in the *tk* locus is not found persuasive. Insertion in the *tk* locus is only one embodiment in Martuza et al. As

indicated above, Martuza et al. teach that their DNA construct comprising in order *lacZ*, tissue-specific promoter, and the ICP4 gene can be inserting into other loci in the HSV genome; such a vector would necessarily have an intact *tk*. Inserting the DNA fragment into the RR locus was, however, known in the prior art (see Chung et al.) and therefore, it would have been within the abilities of one of skill in the art to use the RR locus to insert the DNA fragment; one of skill in the art would have been particularly motivated to use the RR locus because Martuza et al. teach that RR inactivation results in a vector which is more sensitive to ganciclovir and less likely to proliferate in normal cells. It is the combination of Martuza et al. and Chung et al. which teaches insertion into the RR locus. Therefore, the argument that Yamamura et al. teach insertion into the *tk* locus is irrelevant; Yamamura et al. was only cited for teaching the calponin promoter and the 4F2 enhancer. The argument that Chung et al. do not teach how to insert other tissue-specific promoters, e.g., albumin promoter of Martuza, in conjunction with the ICP4 gene and LacZ is not found persuasive. The fact is that Chung et al. teach recombination at the RR locus and the nature of the DNA fragment to be inserted is irrelevant; any fragment can be inserted by following the teachings of Chung et al. At the time the invention was made, homologous recombination was a well-known and widely used technique. Applicant argues that one of skill in the art could not make a construct of Martuza within the RR locus as taught by Chung because any one of the lacZ gene, a cell-specific promoter, and an ICP4 gene may undergo ablation when attempting to construct a herpes viral vector as claimed, or because of the difficulty in cloning the vector even when such a vector with appropriate recombination of the above

three elements has been produced. This argument is not supported by any evidence. Apart from arguments, Applicant did not provide any evidence as to why insertion of a DNA fragment in the *tk* locus would be successful (i.e., lacZ gene, a cell-specific promoter, and an ICP4 gene do not undergo ablation and the recombinant vector is easily obtained by cloning), while the insertion of the same DNA fragment in the RR locus would not be successful. As noted above, at the time the invention was made, homologous recombination was routine in the prior art. Moreover, homologous recombination at the RR locus was already known. Therefore, it would have bee within the abilities of one of skill in the art to obtain the vector according to the combined teachings above. The argument that Martuza et al., Chung et al., and Yamamura et al. do not teach a vector comprising both *lacZ* and EGFP genes is not found persuasive because it is the combination of Martuza et al., Chung et al., Yamamura et al., Wagstaff et al., and Foster et al., which teaches such (see above).

9. Claims 1, 6, 7, 20, 21, 25, 26, 35, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al. taken with each Chung et al., Yamamura et al., Wagstaff et al., and Foster et al. in further view of Miyatake et al. (Stroke, 1999, 30: 2431-2439, of record).

The teachings of Martuza et al., Chung et al., Yamamura et al., Wagstaff et al., and Foster et al. are applied as above for claims 1, 6, 7, 20, 21, 25, 35, and 36. Martuza et al., Yamamura et al., and Chung et al. do not teach therapy by targeting the virus to proliferating smooth muscle cells (claim 26). However, at the time the invention

was made, therapy by specific targeting proliferating smooth muscle cells was taught by the prior art. For example, the prior art teaches using tissue specific replication competent HSV vectors to inhibit smooth muscle cell proliferation (see Miyatake et al., the whole paper). One of skill in the art would have known, would have been motivated, and would have been expected to have a reasonable expectation of success in using the vector taught by Martuza et al., Yamamura et al., and Chung et al. (i.e., replication competent and, since calponin is highly expressed in proliferating smooth muscle cells, specific for proliferating smooth muscle cells) to treat disorders associated with smooth muscle cell proliferation, because the art teaches the usefulness of using such vectors to treat disorders associated with cell proliferation, including those characterized by smooth muscle proliferation.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Miyatake et al. do not cure the deficiencies of Martuza et al., Chung et al., and Yamamura et al.

Applicant's argument is acknowledged, however, the rejection is maintained for the reasons set forth above.

10. Claims 1, 6, 7, 20, 21, 23-25, 35, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al. taken with each Chung et al., Yamamura et al.,

Wagstaff et al., and Foster et al., in further view of Tjuvajev et al. (Cancer Res, 1998, 58: 4333-4341, Abstract, of record).

The teachings of Martuza et al., Yamamura et al., and Chung et al. are applied as above for claims 1, 6, 7, 20, 21, 25, 35, and 36. Martuza et al., Yamamura et al., and Chung et al. do not teach detecting the *in vivo* distribution of the vector by determining tk activity using positron emission tomography (PET) and FIAU labeled with ^{124}I (claims 23 and 24). Tjuvajev et al. teach the noninvasive imaging of *tk* gene transfer and expression by PET and FIAU labeled with ^{124}I. It would have been obvious, to one of skill in the art, at the time the invention was made, to monitor the distribution and expression of the vector taught by Martuza et al., Yamamura et al., and Chung et al. by using PET and FIAU labeled with ^{124}I, with a reasonable expectation of success. The motivation to do so is provided by Tjuvajev et al., who teach their method as useful for providing the information necessary for monitoring clinical gene therapy. One of skill in the art would have been expected to have a reasonable expectation of success in using such a method because the art teaches the successful use of the method to monitor transgene expression.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Tjuvajev et al. do not cure the deficiencies of Martuza et al., Chung et al., and Yamamura et al.

Applicant's argument is acknowledged, however, the rejection is maintained for the reasons set forth above.

11. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

/Ileana Popa/
Art Unit 1633